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14. ABSTRACT The purpose of this study is to determine the safety and tolerability of topiramate (TPM) in the treatment of early seizures following traumatic brain injury (TBI), and to compare the efficacy of TPM to prevent early seizures to the standard of care (phenytoin). A secondary objective is to obtain the data necessary to design a randomized clinical trial to determine if TPM can prevent epilepsy and improve neurological outcome after TBI. In the first two years of the study, we formulated the protocol and all documents required by regulatory bodies. These were approved by the IRB at the University of Pennsylvania, HSRRB at the USArmy, and the FDA. The infrastructure for the study was established, relevant personnel were hired and the patient recruitment methods, interactions with the trauma center, neurosurgical services, EEG laboratory, pharmacy, etc. were organized in order to conduct the research. Patient recruitment was begun but after screening more than 100 prospective patients with TBI, no patients were able to be admitted to the study as it was constituted, for several unforeseen technical reasons. The protocol has been revised to eliminate these obstacles. In addition, a NINDS-sponsored workshop on Biomarkers for Epileptogenesis was held and a program of new potential biomarkers was incorporated into the study.					
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INTRODUCTION:

The purpose of this study is to determine the safety and tolerability of topiramate (TPM - Topamax®) in the treatment of early seizures following traumatic brain injury (TBI), and to determine if topiramate can prevent early seizures better than the current standard of care (phenytoin). A secondary objective is to obtain the data necessary to design a randomized clinical trial to determine if topiramate can prevent epilepsy and improve neurological outcome after TBI. In addition, the study proposed to help identify biomarkers for the process of epileptogenesis that could be used to predict which patients with TBI were most likely to develop posttraumatic epilepsy, and as an assay for effects of potential therapies. Approximately 90 patients at the University of Pennsylvania will participate in this study. Patients with moderate to severe head trauma who meet entry criteria will be randomized to one of three arms of the study. All patients will receive a loading dose of phenytoin within several hours of being admitted to the trauma/neurosurgical unit, as part of the standard of care for such individuals. The patients will then be randomized to three experimental arms. One arm will receive topiramate for six days, the second arm will receive topiramate for three months, and the third, control arm will continue to receive phenytoin for six more days (current standard of care). EEGs will be performed as soon as possible continuously for seven days from onset of the study. The patients will be monitored for clinical seizures, subclinical, electrographic seizures, and recovery of function. Additional EEG analyses will examine potential biomarkers for epileptogenesis. Blood samples, and where possible without additional invasive procedures, CSF samples, will be collected and stored for analysis of possible biochemical biomarkers of epileptogenesis. Patients will also have MRI scans at one month and twelve months to assess structural damage to the brain. Patients will be followed for two years to determine if epilepsy subsequently develops and to assess level of functional recovery.

BODY:

The original Statement of Work indicated three sets of projects to be accomplished in the first two years of the grant. We have completed most of these objectives.

In the first year of the study, we formulated the protocol for the clinical trial, created case report forms and case books, and developed the informed consent documents and other documents required by regulatory bodies. All of these were submitted to the IRB at the University of Pennsylvania, the US Army HSRRB, and the FDA. The approval process for this protocol, especially from the HSRRB, took approximately one year. During this time we established the infrastructure for the study, hired relevant personnel and organized the patient recruitment methods, interactions with the trauma center, neurosurgical services, EEG laboratory, pharmacy, etc. in order to conduct the research. Patient recruitment is now commencing.

Once all the regulatory and infrastructural issues were accomplished, we began attempting to recruit patients for the study.

Below we present the original SOWs (in italics) and our accomplishments over the first two years:

SOW - Task 1: *Develop instruments for a pilot (and subsequently, full) clinical trial for epilepsy prevention after head injury.* This has been accomplished by the development of the clinical trial protocol, informed consent, case books, and regulatory documents. All of these have received approvals by the University of Pennsylvania IRB, the USArmy HSRRB, and the FDA. This approval process took approximately one year to complete. The most prolonged component was the HSRRB.

- a. *Develop the web-based clinical trial instrument now being tested at the University of Pennsylvania for use in clinical trial for epilepsy prevention after head injury. (This study*

management tool will act as the primary system for managing all aspects of the clinical trial, including functioning as a central repository of all research studies and associated personnel, budget set-up and financial tracking, self-population of standard forms, tracking of IRB and other regulatory approvals, subject scheduling and processing, and overall study tracking. It is expected that once this instrument is fully implemented for this neuroprotection study, it will be easily reformulated for other neuroprotection trials.) We have accomplished this task but have not yet incorporated the web based clinical trial instrument. Instead, we developed these tools internally. We expect to attempt to employ a web based mechanism as the trial progresses. We have been investigating several software packages designed specifically for use in clinical trials of various sizes, that would be suitably powerful, but also suitably “user friendly” to permit study personnel to enter data efficiently and also permit continuous data monitoring and evaluation. We recently purchased licenses for the Science Trax Software package (Study Trax). This software is especially designed for use in research. Users can easily learn and adopt the application. The analytical process is streamlined because the user has the ability to create analysis-ready data sets that export to statistical packages. This eliminates the dependency on technical staff to create and export data and it also reduces the burden on the staff by allowing the subjects to enter data via the internet.

- b. *Develop web-based clinical data base for use in epilepsy prevention trial.* Similarly, we chose to use a simpler, more easily available data base for the early pilot program, as the expense for developing a more comprehensive web-based data base was beyond our budgetary capacity.
- c. *Develop brain image data base (BRAID) that can be combined with the clinical data base for use in epilepsy prevention trial.* We have established appropriate MRI protocols for the TBI study in collaboration with the neuroradiology group at the University of Pennsylvania to permit collection of MRI data on the TBI patients in the study and incorporate these images into a BRAID data base being developed at the University.
- d. *Combine instruments developed in above into a specific clinical protocol for a 3 arm study designed to prevent epilepsy after moderate to severe head injury.* This has been accomplished and has passed all regulatory requirements.

SOW - Task 2: *Develop the infrastructure for implementation of randomized double blind trial to prevent epilepsy after head injury.* This has been accomplished.

- a. *Establish procedures with trauma team and ER personnel for identifying candidates for epilepsy prevention trial.* We have mobilized collaborators in the ER, the Trauma Unit, and our newly established Neurological/Neurosurgical Intensive Care Unit to participate in the study. We have held a number of meetings with the teams to provide in-service training and will continue to do so as the protocol launches. Most specifically, we are utilizing a unique resource here at the University of Pennsylvania to identify potential subjects and notify study personnel. Our ER has established a program whereby talented and highly motivated premedical students work in our ER every day and night to identify candidates for various clinical trials that originate in the ER. They are being trained to identify suitable candidates for our TBI study and will notify us as soon as such patients reach the trauma bay in the ER.
- b. *Establish procedures to obtain appropriate consent from patients that are too impaired to provide conventional informed consent. This would involve obtaining consent from individuals who are legally identified as being able to provide consent or by obtaining community consent.* This has been accomplished to the satisfaction of all regulatory bodies involved. This is not a trivial issue, since most of the patients will arrive to the ER in a state that will prevent them from being able to provide informed consent (e.g. either comatose or mentally impaired). As mentioned above, our initial protocol required administration of the first dose of antiseizure drug by 12 hours from the TBI, so we needed to reach the appropriate, legally sanctioned individual associated with each patient to provide informed consent. This could not be done

with either waiver of consent, or “community consent” under current HSRRB guidelines, and we were not permitted to obtain informed consent over the telephone, even temporarily. Thus, we had to rely on being able to communicate directly with appropriate surrogates within 12 hours of the TBI. This required that our study personnel, mainly physicians and EEG technologist, be available 7 days per week, 24 hours per day. As mentioned above, it turned out to be virtually impossible to identify perspective candidates for the study and identify appropriate individuals for obtaining informed consent in person, within the guidelines initially established, as especially as individuals with TBI often presented late at night, on weekends, and with appropriate “consenters” unavailable. As discussed above, for this and other reasons, the protocol has been revised.

- c. *Develop and promulgate standardized treatment protocol for head injured patients.* This was accomplished in collaboration with our neurosurgical team.
- d. *Establish pharmacy program for administration of study medications in a double blind manner.* This was accomplished with the HUP Interventional Drug Services.
- e. *Establish procedures for obtaining continuous EEG monitoring for 7 days post head injury.* This was accomplished by recruiting a talented EEG technologist to perform and monitor these tests and be dedicated to this protocol. She already has experience performing continuous EEGs on TBI patients from a preliminary study (without drug intervention) that we have begun at the University of Pennsylvania. In addition, we are using EEG electrodes that are CT and MRI compatible so they will not need to be removed each time a patient with TBI requires an emergency study as part of their clinical care. These electrodes are part of the standard care for patients in the Neurological Intensive Care Unit who are on continuous EEG monitoring.
- f. *Establish internal and external data and patient safety monitoring boards.* We have an internal safety review process and are in the process of establishing an external DSMB. This is not required by the regulatory bodies, but we thought it would be a useful addition to the study.

SOW - Task 3: *Implement pilot clinical trial to prevent the development of epilepsy in individuals with moderate to severe head injury by 7 day and 3 month treatment with topiramate*

- a. After receiving approval from all the relevant regulatory agencies, we began to screen TBI patients arriving in the trauma unit of the Hospital of the University of Pennsylvania for entry into the study. At this point we encountered two major and unexpected problems. First, because of our inability to enter patients into the study based on either a waiver of informed consent or community consent, we needed to have a personal interaction with the legally designated representative of the patient with TBI in order to obtain informed consent to enter them into the study. Because moderate to severe TBI often results in impaired consciousness, judgment and cognitive function, we most often were unable to obtain informed consent from the patients, themselves. This proved to be exceedingly difficult within the original 12 hour window for admission that was initially established. Secondly, although before the study had begun, we analyzed initial treatment of TBI patients at HUP and determined that many, for a variety of legitimate reasons, did not receive phenytoin within the first 12 hours, once the study commenced and administration of an antiepileptic drug became part of the protocol for all patients with moderate to severe TBI, it was impossible to withhold phenytoin for the 12 hours during which informed consent, randomization, medication distribution, etc was occurring in the protocol. Third, a significant number of patients arrived at HUP close to, or just after, the 12 hour window, so they could not be recruited for the clinical trial.
- b. After screening more than 100 patients over the first 6 months after the protocol was approved, we determined that the pilot program would need to be modified in order to accomplish its goals. Accordingly, we submitted a revised protocol to the IRB at the University of Pennsylvania, the FDA and the USArmy HSRRB. The revised protocol now allows all

patients to receive a loading dose of phenytoin within 3 hours of being admitted to the trauma unit (standard of care), allows for a 24 hour window for admission to the study, and lowers the initial, loading, dose of topiramate. The remaining elements of the pilot trial remain as they were. We are confident that these changes will permit recruitment to proceed.

- c. The IRB at the University of Pennsylvania approved the protocol modification quickly. The FDA has done the same. We are currently awaiting approval from the USArmy HSRRB so that we can commence with recruitment. We are hoping that this will occur quickly, since, if anything, the revised protocol represents even less risk to the patients than the original protocol.

KEY RESEARCH ACCOMPLISHMENTS:

- Write clinical protocol
- Develop informed consents
- Develop case report forms
- Explore various software packages designed for developing clinical trial data bases
- Submit documents to University of Pennsylvania IRB and obtain approval
- Submit documents to US Army HSRRB and obtain approval
- Submit documents to FDA and obtain IND
- Recruit EEG technologist
- Arrange for randomized drug distribution with Pharmacy
- Arrange collaborative efforts with emergency room, neurosurgery and trauma units
- Establish mechanism for rapid identification of subjects upon arrival in trauma unit
- Develop in service training for relevant personnel
- Establish brain imaging protocols
- Revise protocol, informed consent and case report forms based on initial unsuccessful recruitment period.
- Organize and lead an NINDS sponsored workshop on Biomarkers for Epileptogenesis
- Identify electrophysiological, imaging, biochemical and genomic biomarkers that might be useful in monitoring the process of epileptogenesis and the response to potential therapies

REPORTABLE OUTCOMES:

To date, there are no reportable outcomes, as the clinical trial protocol is just getting launched. The results of the Biomarkers for Epileptogenesis workshop will be presented in March, 2007 at the 9th biannual Antiepileptic Drug Trials meeting to be held in Sunny Isles, Florida. Several of the conclusions from this workshop will be incorporated as NINDS guidelines in the Curing Epilepsy Conference that will be held in Bethesda, MD in March 2007.

CONCLUSION:

In the first year of this grant we successfully completed all the pretrial components and received all the necessary regulatory approvals. This included performing 7 days of continuous EEGs on TBI patients who were not part of this research protocol and who did not receive any specific anti-epileptogenic seizure intervention beyond current standard of care. Developing the infrastructure for this kind of trial and successfully navigating all the potential issues in an acute intervention trial in

severely injured patients was not a trivial task. Similarly, coordinating multiple medical teams, each of which is focused on their own tasks with regard to major trauma cases (e.g. trauma surgeons, neurosurgeons, emergency room personnel, nurses, pharmacy, etc.) was also a significant accomplishment. By the middle of the second year we attempted to begin recruiting patients. After screening more than 100 TBI patients in our trauma unit over six months, we realized that there were major procedural obstacles to completing the pilot trial as originally formulated (see SOW - Task 3, above) and have modified the protocol to circumvent these problems without compromising the study. This protocol modification has already been approved by the University of Pennsylvania IRB and the FDA. We are awaiting approval from the USArmy HSRRB.

One additional disappointment at present relates to establishing a more general, comprehensive data base that would be used in this study and would then be available for other studies of anti-epileptogenesis and neuroprotection. To do this on a large scale and to incorporate all the elements needed that would allow the data entered into such a data base to meet FDA standards for drug or treatment registration was much more expensive than we had estimated in our initial proposal. We knew that we had underestimated this expense but it was necessary to keep our budget under the DOD cap. That level of funding would just about allow the accomplishment of the pilot trial. Thus, we are now utilizing a simpler data base designed for clinical trials for our current activities with the hope that it will be transposed into the more sophisticated data base when our pilot trial is completed and/or when additional funding becomes available.

By contrast to our mild disappointment about the data base development, we have achieved a more significant accomplishment with regard to a very important issue related to this study and one which was not submitted as a major part of this grant. We initiated a program in conjunction with the National Institutes of Neurological Diseases and Stroke to hold a conference on biomarkers of epileptogenesis. Our reasoning was that we were developing a unique resource for trying to study this issue in humans as an adjunct to our study and with no additional risk to our patients. We are collaborating with the only two groups in the US who have been, or are currently, engaged in epilepsy prevention trials – The University of Washington (who recently completed their third, unfortunately negative, clinical trial to prevent epilepsy after TBI) and a group in Washington, DC launching a small pilot trial of preventing epilepsy after TBI (although with less severely injured patients than we are studying and without continuous EEG recordings). This conference brought together researchers at both the clinical level and animal model level to consider what is known about the process of epileptogenesis and how we might develop biomarkers of the process using electrophysiology (including highly sophisticated signal processing techniques that are not standard in this field), imaging, biochemical markers in CSF and serum, and genomics.

REFERENCES: N/A

APPENDICES: N/A

SUPPORTING DATA: N/A